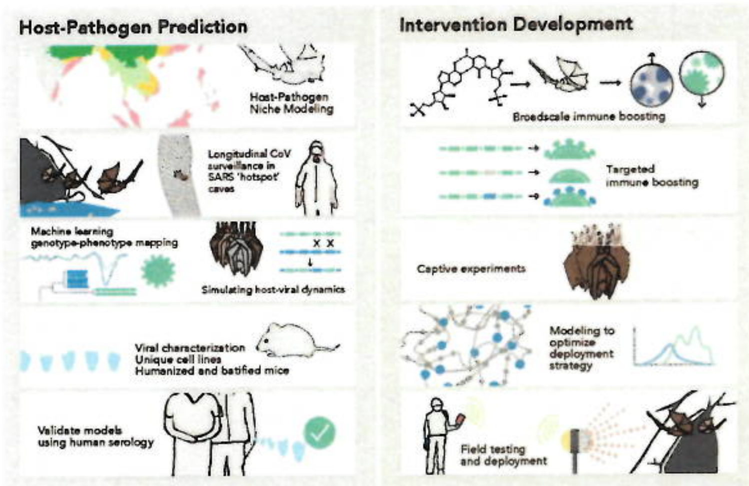
Executive Summary: DEFUSE

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CONCEPT



APPROACH

Host-Pathogen Prediction:

- Integrated field sampling, viral characterization, modeling: In-depth sampling of bat SARSr-CoVs in high-risk site of active spillover, Yunnan, China. Sptial models using bat and viral data to estimate SARSr-CoV jump potential across Asia. 'Spatial viral spillover risk' Mobile App. of background viral jump risk across Asia.
- Experimental assays to test QS_0 jump potential: Sequence QS_0 spike protein similarity to high-risk SARSr-CoVs, model spike structure to assess ACE2 binding, then *in vitro* and ACE2 humanized mouse experiments. Use results to test machine-learning genotype-to-phenotype model predictions of viral spillover risk.
- Genotype-phenotype models: Models to estimate evolutionary/recombination rates, capacity to generate future QS capable of human infection, based on spike protein diversity, recombination frequency etc.
- Validation with previously-collected human sera: Use LIPS assays that target specific SARSr-CoV spikes to identify spillover of these strains in a high-risk population in Yunnan, China.

Intervention Development:

- (1) Broadscale immune boosting: Inoculate bats with immune modulators to upregulate their naturally-inhibited innate immunity and suppress viral replication, transiently reducing viral shedding/spillover risk.
- (2) Targeted immune boosting: In concert with above, inoculate bats with novel chimeric polyvalent recombinant spike proteins to enhance their adaptive immune memory against specific, high-risk viruses.
- Viral dynamics: Develop stochastic simulation models to estimate the frequency, efficacy, and population coverage required for intervention approaches to effectively suppress the viral population.
- Field trial: Use team expertise in wildlife vaccine delivery (transdermal nanoparticles, raccoon poxvirus vector) to develop effective molecule delivery via automated aerosolization onto bats at roost entrance at our three test cave sites in a cave complex in Yunnan, China, where SARSr-CoVs have infected people.

IMPACT

- Security concerns across Asia make the region a potential deployment site for US warfighters. Troops face increased disease risk from SARSr-CoVs, which are shed via urine and feces as bats forage at night.
- Our work in Yunnan, China shows that: 1) bat SARSr-CoVs exist that can infect human cells, produce SARS-like illness in humanized mice, and are not affected by monoclonal or vaccine treatment; and 2) bat SARSr-CoV host-jump into local human populations is frequent. These viruses are therefore a clear and present danger to US defense forces in the region and global health security.
- Our goal is to analyze, predict, then "DEFUSE" the spillover potential of novel bat-origin high-risk SARSr-CoVs in Southeast Asia and across these viruses distribution. This will safeguard the US warfighter, reduce risk for local communities and their livestock, improving food and global health security.
- Our strategy is based on immune parameters that are found across all bat taxonomic groups. If successful, the DEFUSE approach can be adapted to MERS-CoV in the Middle East, other SARSr-CoVs in Africa, and other high-impact bat-origin viruses (e.g. Hendra, Nipah, Ebola, Marburg viruses).

	Phase I	Phase II	Total
Proposed	$8,411,546	$5,797,699	$14,209,245

☒Human Use/ ☒ Animal Use

CONTEXT

- No technology exists to reduce exposure to novel bat CoVs. No effective therapeutics or countermeasures for SARS-CoV, related CoVs, or other bat viruses (Ebola, Marburg, Nipah, Hendra etc).
- Our team has conducted pioneering research modeling disease emergence, understanding CoV virology, bat immunity, and wildlife vaccine delivery. Previous work provides proof-of-concept for: 1) predictive 'hotspot' modeling; 2) upregulating bat immune response through the STING IFN pathway, 3) recombinant chimeric spike-proteins from SARSr-CoVs; 4) molecule delivery to wildlife incl. bats.
- DEFUSE approach is based on immunological pattern found across bat families, therefore will be broadly effective, scalable, economical and achievable in the allotted time frame. It poses little environmental risk, and presents no threat to the warfighter, or non-target populations.
- Immune modulation is more likely to be effective than CRISPR-Cas9 gene drives because bats are relatively long-lived, highly mobile, and have long inter-generational periods (2-5 years) with low progeny (1-2 pups). Furthermore, gene drive technology could have negative ecological consequences and its effectiveness will be hard to evaluate within the defined Period of Performance.